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TWO NEW XENICIN DITERPENOIDS FROM THE OCTOCORAL ANTHELIA EDMONDSONI

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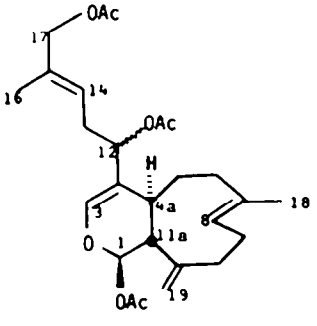
Abstract -- From the soft coral Anthelia edmondsoni two new diterpenoids, waixenicin-A (1) and -B (2) have been isolated. Their structures were elucidated by ^{1}H and ^{13}C NMR analysis and the relative stereochemistry was determined by x-ray diffraction of crystalline waixenicin-B (2).

A delicately beautiful blue soft coral Anthelia edmondsoni (Family Xeniidae) was first described from Hawaii.[1] Observations[2] that two nudibranchs, Tritonia hawaiiensis and Pteraeolidia ianthina, feed on Anthelia led us to search for these animals so that we might study their chemistry. We succeeded in locating A. edmondsoni on the north shore of O'ahu, but not its alleged predators. From the octocoral we isolated two new xenicin diterpenoids, whose structures we report.

Since the first isolation of a xenicin diterpenoid, i.e. a trans-fused cyclononane-dihydropyran by the Oklahoma group[3] numerous representatives of this class of compounds have been reported from soft and horny (Gorgonian) corals. Kashman and coworkers[4,5] have recently summarized this research. The distinctive feature of the new compounds, waixenicin-A (1) and -B (2)[6] is their oxygenation at C-10 and C-17.[7]

Isolation of waixenicin-A from the freeze-dried animals was carried out by hexane extraction, followed by partition of the hexane extract with aqueous methanol. Successive chromatographies of the hexane fraction on BioBeads SX-8, silica, and reversed phase HPLC led to pure 1 (0.17% from dry animal), an oil, $[\alpha]_D$ +62.7°. Waixenicin-B was obtained by extracting the animals after the hexane treatment with methanol/ethyl acetate (1:1). The residue was taken up in aqueous methanol and partitioned with hexane, then with chloroform. Chromatography of the chloroform residue, first on BioBeads SX-8, then by reversed phase HPLC led to pure 2 (0.23% from dry animal), mp 124-125°C, $[\alpha]_D$ = +17.5°.



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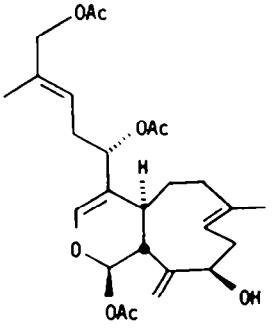

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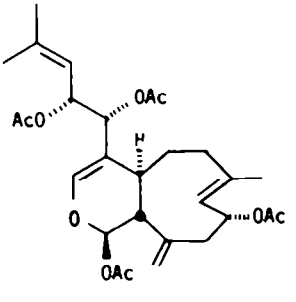

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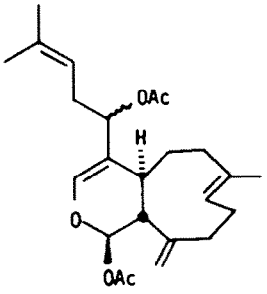
Several features of the ^{1}HNMR ($CDCl_3$) spectrum of 1 are characteristic of the xenicins: two fine doublets at δ 6.47 (H-3) and 5.84 (H-1), singlets at δ 4.84 and 4.74 (H_2-19), and a 3H multiplet at δ 5.31. In deuteriobenzene this multiplet is cleanly resolved into three apparent triplets (actually doublets of doublets) at δ 5.50 (H-12), 5.42 (H-8), and 5.32 (H-14). Instead of the expected three vinylic methyls only two (δ 1.69, 1.66) could be seen. A third methyl group apparently existed as an acetoxymethylene as seen by a 2H singlet at δ 4.41.

Comparison of the ^{13}C NMR data with those of other xenicins[3,9] showed that the acetoxymethylene is at C-17. The methyl ^{13}C resonances for C-16 and C-17 in xenicin (3) occur at 18.9 and 25.6 ppm. The ^{13}C NMR spectrum of 1 lacks a quartet at a field lower than 21.5 ppm, but exhibits a methyl signal at 14.4 ppm. These data not only place the new acetate at C-17, but agree with the triplet signal at 69.7 ppm (CH_2-17) and with the upfield shift of the C-16 quartet from about 18 to 14.4 ppm due to a γ-effect.[10] The remaining methyl signal at 16.9 ppm can be confidently assigned to C-18. Data for Kashman's 9-deacetoxy-14,15-deepoxyxeniculin (4)[9] and for monoterpene models 5 and 6[11] fully support these assignments (see Table 1).



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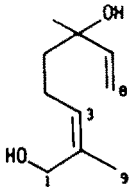

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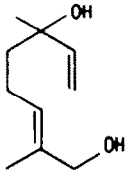

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The remaining acetate was assigned to C-12 on the basis of the 2D ^{1}H-NMR (COSY) spectrum in benzene-d_6. The triplet at δ 5.32 showed couplings to the methyl signal at δ 1.52 (Me-16), the acetoxymethylene at δ 4.41 (CH_2-17), and to two upfield protons at δ 2.45 and 2.30. The triplet at δ 5.42 showed coupling to the methyl at δ 1.54 (Me-18) and to two upfield protons at δ 2.30 and δ 1.95 (CH_2-9). Thus the triplet at δ 5.32 was assigned to H-14; the triplet at δ 5.42 to H-8; and the remaining triplet at δ 5.50 to the acetoxymethine. This proton showed coupling to the same two upfield protons (δ 2.45 and 2.30) as H-14. This signal is therefore assigned to C-12, thus completing the structure of waixenicin-A (1).

The ^{1}HNMR spectrum of waixenicin-B (2) exhibits one additional downfield signal, a doublet at δ 4.44 ppm ($CDCl_3$). It is assigned to a hydroxy methine on the basis of a broad band at 3500 cm^{-1} in the IR spectrum, an m^+/z at 476 (cf 460 for 1) and doublets at 76.7 and 74.6 ppm in the ^{13}C NMR spectrum. Waixenicin-A (1) exhibits only one doublet in this region, at 74.4 ppm.

The 2D ^{1}HNMR spectrum of 2 in benzene-d_6 shows that the hydrogen of the hydroxymethine is coupled to a one proton signal at δ 2.25 and is weakly coupled to one of the exo methylene protons at C-19. The fact that the methine hydrogen adjacent to the hydroxy group is allylic (δ 4.44, $CDCl_3$) and is also coupled to a proton at C-19 indicates that the OH must be at C-10. In Dreiding models of the xenicin ring system an α-C-10 methine hydrogen, as in 2, exhibits dihedral angles of approximately 25° and 90° with the two C-9 hydrogens. If H-10 is β-oriented, the dihedral angles with the C-9 protons are approximately 25° and 145°. Clearly, the ^{1}HNMR data are consistent only with the stereochemistry shown in 2, as H-10 is coupled only to one of the C-9 hydrogens.

Supporting evidence for the C-10 stereochemistry comes from the ^{1}HNMR spectra of 1 and 2 in deuteriobenzene, where the C-18 methyl protons and H-11a are shifted downfield (Table 2). In Dreiding models a β-hydroxy at C-10 is in close proximity to CH_3-18 and H-11a. The fact that the H-11a signal at δ 2.60 is a slightly broadened singlet shows that the coupling to H-4a is very small with a dihedral angle of approximately 90°. This is analogous to previously reported xenicins, all of which have trans-fused rings. The small coupling of 1.6 Hz between H-1 and H-11a requires H-1 to be α.

Attempts to define the remaining stereochemical assignment at C-12 by chemical transformations and spectroscopy were unproductive. Deacetylation with acid (p-TSA) or base ($MeOH/NH_3$) resulted in decomposition of 1. Reaction with $NaBH_4$ or $LiAlH_4$ took place only >50°C, when 1 began to decompose. Pyridinium dichromate oxidation led to a single product, apparently (^{1}HNMR, MS), the 7,8-epoxide. This result is trivial as 1 is readily transformed to this epoxide when it is exposed to air. Ozonolysis at -78°C cleaved only the C-7,8 olefin and left the other double bonds intact. Because of the unpromising results of these experiments, done on a milligram scale, they were not scaled up nor were the products rigorously characterized.

Fortuitously, waixenicin-B (2) could be crystallized from a 2:1 benzene/ethyl acetate solution, into which hexane was allowed to diffuse, and a single crystal was submitted for x-ray diffraction studies.

Preliminary x-ray photographs of waixenicin-B (2) showed monoclinic symmetry. Precise lattice constants, determined from a least-squares fit of fifteen diffractometer measured 2θ-values, were a = 8.545(1), b = 8.166(1), c = 18.721(2) Å, and β = 94.26(9)°. Systematic extinctions, crystal density and the presence of chirality were uniquely accomodated by space group $P2_12_12_1$ with one molecule of formula $C_{26}H_{36}O_8$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a fully automated diffractometer using a variable speed 1° ω-scan and graphite monochromated CuKα (1.54178 Å) radiation. A total of 2050 reflections were scanned in this fashion and after correction for Lorentz, polarization and background effects, 1853 (90%) were judged observed.[12,13] The structure was solved without much difficulty by a multisolution tangent formula approach followed by E- and eventually F_o-syntheses. All 34 nonhydrogen atoms were located in this fashion and most of the hydrogens (27 out of 36) were located on a ΔF-synthesis following partial refinement. The remaining nine hydrogens were included at calculated positions. Block diagonal least-squares refinements with 42 anisotropic nonhydrogen atoms and 36 isotropic hydrogens have converged to a standard crystallographic residual of 0.051 for the observed reflections. The x-ray experiment defined only the relative stereostructure of waixenicin-B (2) so the enantiomer displayed is an arbitrary choice. A computer generated perspective drawing of the final x-ray model is presented in Figure 1.

Acknowledgment -- We thank Dr. Walter Niemczura for acquisition of ^{13}C NMR spectra and Lars Bergknut for the mass spectra. We are especially grateful to Dr. Deborah Roll for her help with collecting A. edmondsoni, acquisition of the COSY ^{1}HNMR spectra, and for many valuable discussions. We are grateful for financial support from Hawaii and New York (Cornell) Sea Grant Programs and from the National Science Foundation.

EXPERIMENTAL PART

Optical rotations were measured on a Rudolph Research Autopol II polarimeter. Mass spectra were recorded on a Varian MAT-311 mass spectrometer. NMR spectra were recorded on a Nicolet NT-300 instrument. Infrared spectra were measured on a Perkin-Elmer 467 spectrophotometer. Ultraviolet spectra were recorded on a Beckman DU-7 spectrophotometer.

Isolation -- A. edmondsoni was collected in September 1982 near Waimea Bay on the north shore of O'ahu and immediately frozen upon removal from the water. The coral was freeze-dried and then repeatedly extracted with hexane to yield 7.66 g of residue from 170.5 g of dried animal. This residue was partitioned between hexane and 90% $MeOH/H_2O$. After removal of the hexane fraction the aq MeOH phase was diluted with H_2O to 60% $MeOH/H_2O$ and partitioned with $CHCl_3$. The $CHCl_3$ residue (2.9 g) was chromatographed on BioBeads SX-8 (column 184 x 4 cm OD) using toluene as eluent. The latter eluting fractions were shown by TLC and ^{1}HNMR spectroscopy to be rich in 1. All fractions containing 1 were combined to yield 1.88 g of residue. Flash chromatography of 530 mg of this residue on silica (solvent gradient, hexane → EtOAc) followed by HPLC (reversed phase, 80% $MeOH/H_2O$) yielded 50 mg of pure 1. Additional amounts of 1 were isolated with 2. Total yield, 295 mg (0.17% of dry coral).

After hexane extraction the coral was repeatedly extracted with MeOH/EtOAc 1:1 to yield 13.8 g of extract. The residue was partitioned between hexane and 90% $MeOH/H_2O$. After removal of the hexane layer the aq MeOH was diluted with H_2O to 60% $MeOH/H_2O$ and partitioned with $CHCl_3$. The $CHCl_3$ portion yielded 5.19 g of residue, of which 2.36 g was chromatographed on BioBeads SX-8 (column 184 x 4 cm OD) using toluene as eluent. The late fractions contained 2 (TLC, ^{1}HNMR) and were combined to yield 883 mg of residue. Reversed phase chromatography on

HPLC of 226 mg of this residue, first with 75% MeOH/H_2O, followed by a second chromatography with 70% MeOH/H_2O, yielded 38.5 mg of 2 and 17.3 mg of 1. Waixenicin-B (2) was dissolved in benzene/EtOAc (2:1) and diffused with hexane to produce x-ray quality crystals. Yield of 2, 387 mg (0.23% of dry coral).

Waixenicin-A (1) -- 0:1, $[\alpha]_D$ +62.7° (c 0.35, MeOH); UV (EtOH): λ_{max} 224 (1158); IR (CCl_4): ν_{max} 2960, 1740, 1370, 1230, 1150, 1010, 940 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 6.47 (1H d, J = 1.8 Hz, H-3), 5.48 (1H d, J = 1.6 Hz, H-1), 5.31 (3H m, H-8, 12, 14), 4.84 (1H s, H-19), 4.74 (1H s, H-19'), 4.41 (2H s, CH_2-17), 2.07 (3H s, OAc), 2.05 (3H s, OAc), 2.03 (3H s, OAc), 1.69 (3H br s, CH_3-16), 1.66 (3H br s, CH_3-18); ^{1}HNMR (C_6D_6): δ 6.54 (1H d, J = 1.7 Hz, H-3), 6.22 (1H d, J = 1.7 Hz, H-1), 5.50 (1H dd, J = 7.4 Hz, H-12), 5.42 (1H dd, J = 7.7 Hz, H-8), 5.32 (1H dd, J = 6.9 Hz, H-14), 4.96 (1H s, H-19), 4.84 (1H s, H-19'), 4.40 (2H s, CH_2-17), 1.70 (3H s, OAc), 1.68 (3H s, OAc), 1.57 (3H s, OAc), 1.54 (3H br s, CH_3-18), 1.52 (3H br s, CH_3-16); ^{13}C NMR (CD_2Cl_2): δ 170.6 s (OAc), 170.1 s (OAc), 169.5 s (OAc), 151.8 s (C-11), 140.8 d (C-3), 136.1 s, 133.2 s (C-7, 15), 124.4 d, 123.7 d (C-8, 14), 116.1 s (C-4), 113.0 t (C-19), 91.8 d (C-1), 74.4 d (C-12), 69.7 t (C-17), 49.6 d (C-11a), 40.3 t (C-6), 37.2 d (C-4a), 35.8 t (C-10), 31.2 t, 30.8 t (C-5, 13), 25.4 t (C-9), 21.5 q (OAc), 21.0 q (OAc), 21.0 q (OAc), 16.9 q (C-18), 14.4 q (C-16); HRMS, m/z 460.2461 ($C_{26}H_{36}O_7$ requires 460.2613); MS: m/z 460(5), 417(3), 401(20), 400(14), 349(21), 342(8), 341(21), 340(9), 333(35), 307(15), 305(48), 298(17), 291(35), 281(31), 280(20), 231(91), 81(100).

Waixenicin-B (2) -- Mp 124-125°C; $[\alpha]_D$ +17.5° (c 0.27, MeOH); UV (EtOH): λ_{max} 221 (2598), 284(368); IR (CCl_4): ν_{max} 3500 br, 2920, 1740, 1370, 1230, 1155, 1020, 945 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 6.49 (1H d, J = 1.8 Hz, H-3), 5.76 (1H d, J = 1.6 Hz, H-1), 5.31 (2H m, H-12, 14), 5.13 (1H dd, J = 8.7 Hz, H-8), 4.94 (1H s, H-19), 4.85 (1H s, H-19'), 4.44 (1H d, J = 5.6 Hz, H-10), 4.40 (2H s, CH_2-17), 2.04 (3H s, OAc), 2.03 (3H s, OAc), 2.01 (3H s, OAc), 1.73 (3H br s, CH_3-18), 1.67 (3H br s, CH_3-16); ^{1}HNMR (C_6D_6): δ 6.56 (1H d, J = 2.0 Hz, H-3), 6.12 (1H d, J = 1.4 Hz, H-1), 5.50 (1H dd, J = 7.4 Hz, H-12), 5.37 (1H dd, J = 6.8 Hz, H-14), 5.22 (1H dd, J = 6.8 Hz, H-8), 4.98 (1H s, H-19), 4.75 (1H s, H-19'), 4.40 (2H s, CH_2-17), 3.99 (1H d, J = 7.3 Hz, H-10), 2.60 (1H br s, H-11a), 1.80 (3H br s, CH_3-18), 1.69 (3H s, OAc), 1.68 (3H s, OAc), 1.54 (3H s, OAc) 1.51 (3H br s, CH_3-16); ^{13}C NMR (CD_2Cl_2): δ 170.6 s (OAc), 170.5 s (OAc), 170.0 s (OAc), 153.6 s (C-11), 141.1 d (C-3), 137.7 s, 133.4 s (C-7, 15), 123.7 d, 121.5 d (C-8, 14), 116.6 s (C-4), 113.7 t (C-19), 92.9 d (C-1), 76.7 d, 74.6 d (C-10, 12), 69.8 t (C-17), 42.4 d (C-11a), 40.7 t (C-6), 37.5 d (C-4a), 35.6 t (C-9), 31.3 t, 30.3 t (C-5, 13), 21.5 q (OAc), 21.2 q (OAc, 21.1 q (OAc), 17.3 q (C-18), 14.5 q (C-16); HRMS, m/z 476.2383 ($C_{26}H_{36}O_8$ requires 476.2410); MS: m/z 476 (<1), 417(10), 416(13), 357(15), 356(11), 349(5), 333(14), 297(25), 296(31), 290(44), 289(86), 267(17), 249(15), 248(66), 247(100).

Table 1. Comparison of ^{13}C Chemical Shift Values (δ) of Some Methyl and Methylene Groups of Waixenicin-A and B with Those of Appropriate Model Compounds

Me \ Compound	1	2	4[a]
C-16	14.4	14.5	18.1
C-17	69.7	69.8	25.7
C-18	16.9	17.3	16.7
	5[b]	6[b]	
C-1	61.8	13.9	
C-9	21.3	68.9	

[a] Ref. 9 [b] Ref. 11

Table 2. ^{1}H NMR Chemical Shift Values (δ) of Some Protons of Waixenicin-A and B in $CDCl_3$ and in C_6D_6

	1		2	
H-	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
16	1.69	1.52	1.67	1.51
18	1.66	1.54	1.74	1.80
11a	~1.95	2.07	2.41	2.60

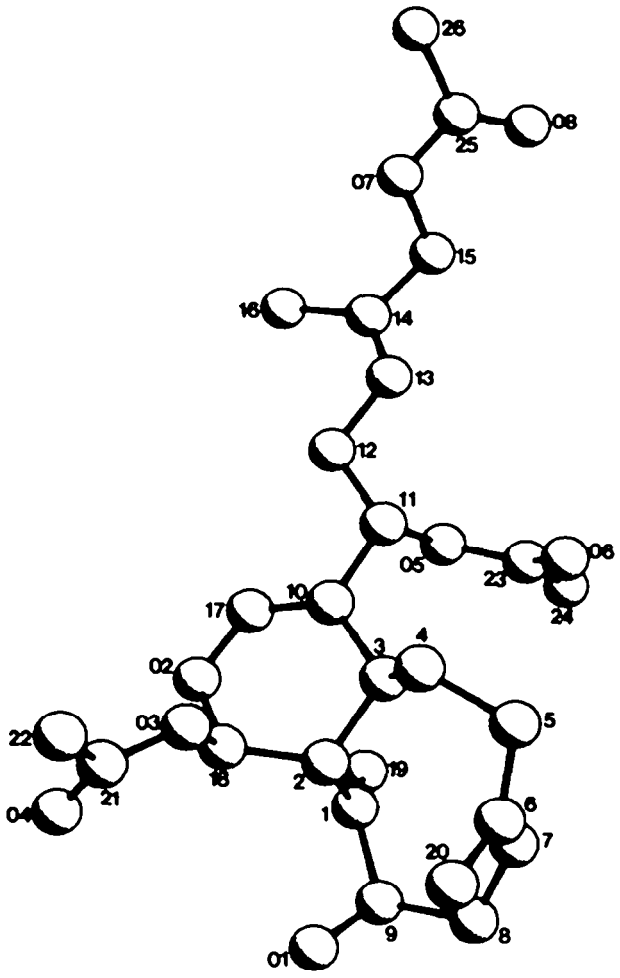

Figure 1. A computer generated perspective drawing of waixenicin-B (2). Hydrogens are omitted for clarity and no absolute configuration is implied.

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6 A. edmondsoni was collected at Waimea bay, O'ahu.

7 We follow the Oklahoma numbering (Ref. 3); Coll and coworkers[8] have, for reasons best known to themselves, introduced an alternate numbering system.

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12 All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78, a system of computer programs for the automatic solution of crystal structures from x-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, University of York, England, 1978; BLS78A, an anisotropic block diagonal least squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

13 The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.